

Case Report

Small Cell Carcinoma of the Ureter with Malignant Lymphoma: Case Report and Literature Review

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A 78-year-old man was referred to our hospital for gross hematuria. Ultrasonography and magnetic resonance urography revealed tumor in the right lower ureter. Computed tomography revealed right cervical lymph node swelling and pathological diagnosis was diffuse large B-cell lymphoma. Right nephroureterectomy was performed and pathologic examination revealed small cell carcinoma of the ureter with a small urothelial cell carcinoma component. As the patient had concomitant other malignancies, additional systemic chemotherapy was not performed. As of 3 months after operation, postoperative course has been uneventful. Only 11 cases of primary small cell carcinoma of the ureter have been described.

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Introduction

Small cell carcinoma is a high-grade malignant neoplasm usually found in the lung, although lesions in other organs have been reported.¹⁻³ In the urinary tract, the urinary bladder is the main area of occurrence.³⁻⁹ Primary ureteral small cell carcinoma is extremely rare.^{1,5,7-10}

We report herein a case of primary ureteral combined small cell carcinoma and malignant lymphoma. To the best of our knowledge, this is the first report of primary ureteral small cell carcinoma combined with malignant lymphoma.

Case report

A 78-year-old Japanese man was referred to our hospital with gross hematuria. He had experienced several recurrences of bladder urothelial cell carcinoma (UCC) and chronic renal failure at a previous hospital. Transurethral resection of bladder tumor (TUR-Bt) and adjuvant intravesical perfusion therapy had been performed for

recurrent noninvasive bladder tumor. However, the 5th recurrence of bladder tumor had progressed to the pT4 stage, and TUR-Bt and radiotherapy (60 Gy) were performed because the patient declined radical surgery.

7 months after, gross hematuria reappeared and the patient was referred to our hospital. Cystoscopy revealed no recurrence in the bladder, but hematuria was confirmed from the right ureteric orifice. ultrasonography revealed right hydronephrosis. A catheter for retrograde pyelography could not be placed into the right ureteric orifice. Magnetic resonance urography revealed a severe stenosis from the right distal ureter to the ureter-bladder junction and ureter tumor with extra-ureter invasion was suspected (Figure 1).

Laboratory testing revealed that hemoglobin was 7.0 g/dl, hematocrit was 22.9% and serum creatinin was 6.0 mg/dl. Physical examination and computed tomography revealed right cervical lymph node swelling, and pathological diagnosis of the biopsy specimen was diffuse large B-cell lymphoma. Pathologically, medium-to-large atypical lymphocytes had proliferated in diffuse fashion (Figure 2a). Tumor cells showed positive results for L26 (Figure 2b) and CD79a and negative results for UCHL-1 and CD3.

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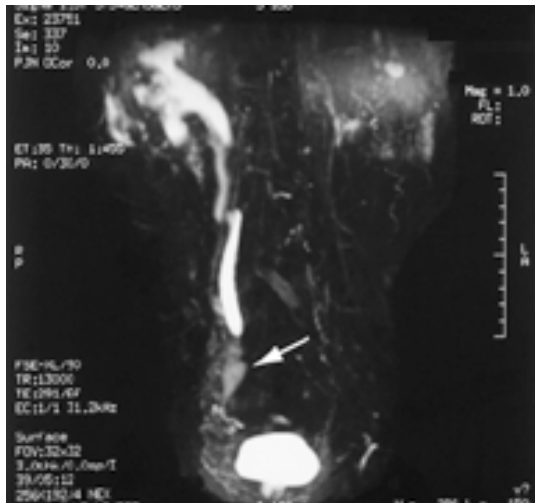


Figure 1. MR urography. Right hydronephrosis and right hydroureterosis are seen. The right distal ureter to ureter-bladder junction shows severe stenosis by a mass lesion (arrow). No lymph node swelling or ascites are apparent.

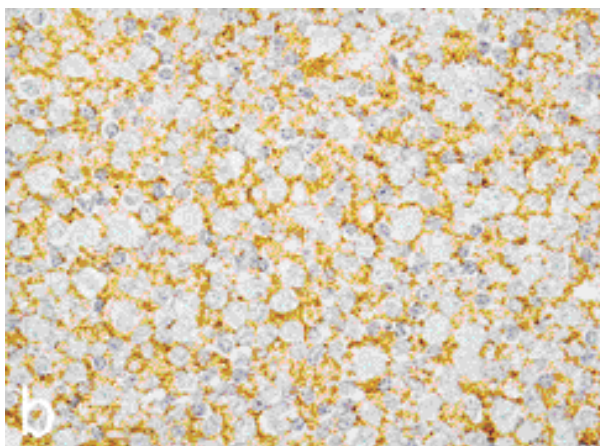
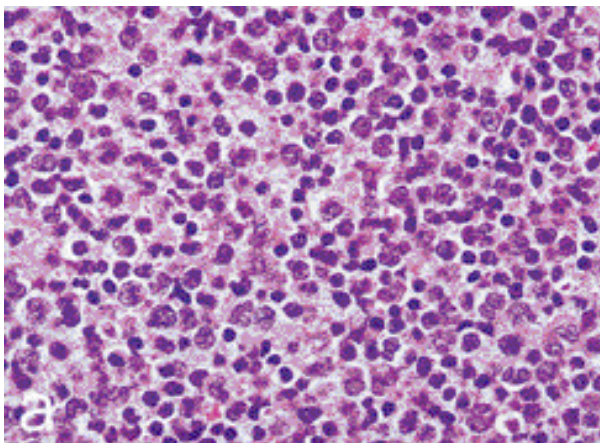


Figure 2. Histopathology of the cervical lymph node biopsy. **a.** Round atypical cells with convoluted nuclei are proliferating in a diffuse pattern without follicular structures (HE, $\times 500$). **b.** Immunohistochemical staining for L26 shows positive cytomembranous reaction in the medium-to-large sized atypical cells ($\times 500$).

During hospitalization, frequent blood transfusion was necessary for severe gross hematuria from the ureteral lesion. Right nephroureterectomy appeared warranted to control hematuria, and was performed after informed consent was obtained.

On gross examination of the ureter, the distal end of the resected ureter showed mural thickening measuring 5 \times 2 cm with mucosal small polypoid changes (Figure 3a). The tumor was hard and the cut surface was solid and gray (Figure 3b).

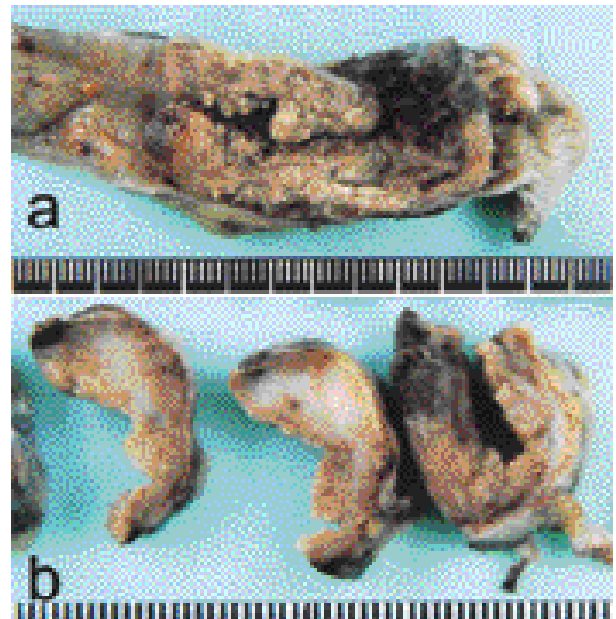


Figure 3. Gross finding of ureter tumor. **a.** The distal end of the resected ureter show mural thickening measuring 5 \times 2 cm with mucosal small polypoid changes. **b.** The tumor is hard and the cut surface was solid and gray.

Histopathologically, the thickened ureteral wall was occupied by the tumor cell infiltration (Figure 4a). The tumor consisted of small cells with round to spindle-shaped atypical nuclei, high nucleus/cytoplasm ratio, and proliferation in solid, cord-like and rosette patterns (Figure 4b). Tumor cells were positive for AE1/AE3, EMA, N-CAM and chromogranin A, and were negative for synaptophysin and S-100. At the periphery of the main tumor, there were different area of the tumor morphology consist of tumor cells with low nucleus/cytoplasm ratio, showing papillary multilayered growth pattern, consistent with conventional UCC (Figure 4c). From these histopathological observations, the lesion was diagnosed as combined small cell carcinoma and UCC, pT3. A regional retroperitoneal lymph node metastasis was identified near the ureter-bladder junction.

Since the patient displayed concomitant malignant lymphoma and was undergoing hemodialysis for chronic renal failure, additional systemic chemotherapy was not performed. As of 3 months after operation, postoperative course has been uneventful.

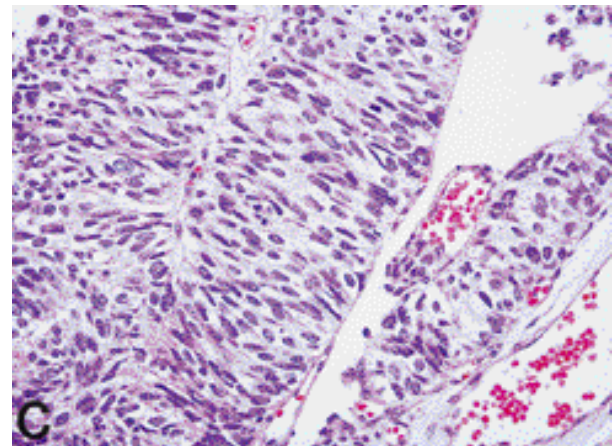
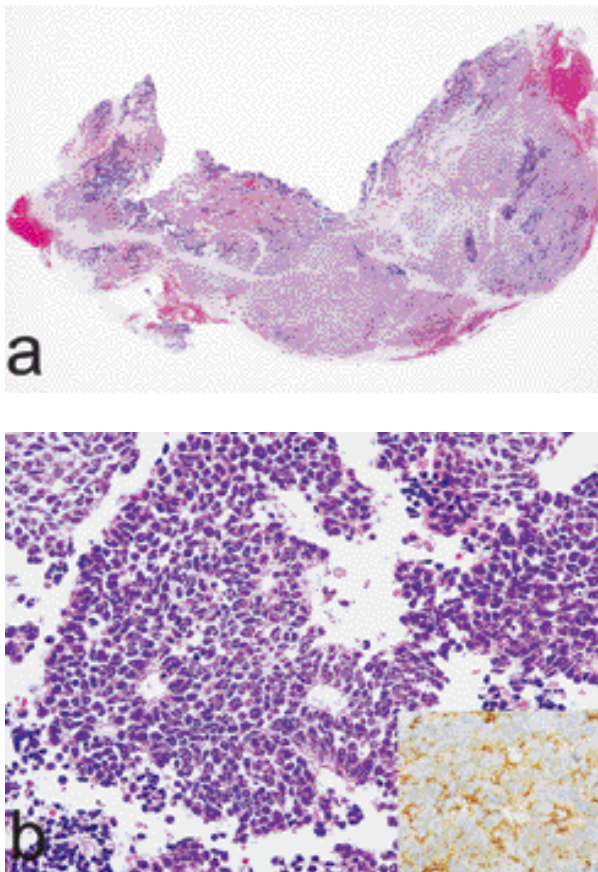


Figure 4. Histopathology of ureter tumor.

a. The thickened ureteral wall is caused by the tumor cell infiltration (HE, scanning magnification).

b. The tumor cell consist of small cells with round to spindle-shaped atypical nuclei high nucleus/cytoplasm ratio, nuclear molding, and proliferation in solid, cord-like and rosette patterns (HE, $\times 250$). Inset: The tumor cells are positive for N-CAM ($\times 250$).

c. There are different area of the tumor cells with low nucleus/cytoplasm ratio, showing papillary multilayered growth pattern, consistent with conventional UCC (HE, $\times 250$)

Discussion

Small cell carcinoma is a highly malignant pulmonary tumor that can also arise in extra-pulmonary sites such as the esophagus, stomach, intestine, trachea, larynx, gallbladder, salivary glands, skin, pancreas, prostate, kidney and urinary bladder.¹⁻³ The urinary bladder is the most common site for small cell carcinoma of the urinary tract.³⁻⁹ Primary ureteral small cell carcinoma is extremely rare.^{1,5,7-10}

In the report of 180 urinary tract small cell carcinomas by Mackey et al., tumor was located in bladder in 106 cases, prostate in 60, kidney in 8 and ureter in only 6.³ Primary ureteral small cell carcinoma excluding the renal pelvis and ureteropelvic junction has only been reported in 11 cases, including the present.^{1,5-13} Patients comprised 8 men and 2 women, with sex not mentioned in the remaining 1 case. Mean age was 67.8 years (range, 53-86 years). Side preponderance was not appeared. The distal area of the ureter is the most frequent site of occurrence (Table 1). The majority of patients have been Asian. Some genetic or other unknown factor may result be associated with this lesion in Asian people.

Hematuria and pain are frequent symptoms for ureteral small cell carcinoma. Hematuria is thought to result from vascular invasion, indicating worse prognosis.¹⁴ Pain might be caused by hydronephrosis following obstruction or narrowing of the ureter.¹⁴ When such symptoms appear, stage may already be high.^{1,5-13}

In the 11 cases of ureteral small cell carcinoma, 5 displayed

components of UCC, including the present case, and 2 cases displayed UCC and squamous cell carcinoma components^{10,11} and 1 case exhibited multiple components of UCC, squamous cell carcinoma, adenocarcinoma, chondrosarcoma and leiomyosarcoma.⁶

Regarding the origin of neuroendocrine tumor in the ureter, two theories have been put forward for small cell carcinoma: malignant change of aberrant neural crest cells; or neuroendocrine transformation of multipotential epithelial reserve cell.¹ The existence of frequent combinations with UCC or other histology supports the latter theory.

In our case, the patient had a history of radiotherapy of the urinary tract. Sinonasal small cell neoplasm 18 years after radiotherapy for retinoblastoma has been reported.¹⁵

Complication of ureteral small cell carcinoma by other malignancies has not been reported previously. The patient in the present case displayed double malignancy, with malignant lymphoma and ureteral combined small cell carcinoma with UCC, which could be a very rare incidental coincidence which had not been reported previously.

Systematic therapy for urinary tract small cell carcinoma is selected as with pulmonary small cell carcinoma, such as cisplatin and etoposide therapy and radiotherapy. Preoperative confirmation of ureteral small cell carcinoma is not easy. For those reasons, surgery has been selected in all reported cases of ureteral small cell carcinoma. Adjuvant radio- and chemotherapy were performed in most cases.

Table 1. The characteristics of reported ureteral small cell carcinoma

Author/ year	Age/Sex	Race	Symptoms	Location	Histology	Stage	Metastasis	Combined disease	Therapy	Prognosis
Sakai ¹ 1990	62M	J	H	L P	SmCC+UCC	pT2	Lymph node	No	NU+EP	8 months, alive with no recurrence
Sakamoto ⁹ 1993	64F	J	FP	L D	SmCC+UCC	pT4	No	No	NU+TC+ CAP	8 months, alive with no recurrence
Tsutsumi ⁶ 1993	60M	J	H	R D	SmCC+UCC+ SqCC+AC+ CS+LS	pT3	No	No	NU+PC+ Rad+EP	16 months, alive with metastasis
Nonaka ⁹ 2001	86M	J	H	R D	SmCC	pT3	No	No	NU+Rad	6 months, dead of cancer
Kim ¹⁰ 2001	60M	K	FP	R D	SmCC+UCC+ SqCC	pT3	No	urinary tract stone	NU	3 years, alive with no recurrence
Ishikawa ¹¹ 2004	53M	J	FP	L M	SmCC+UCC+ SqCC	pT3	Lymph node	No	MEC+NU	8 months, dead of cancer
Chang ¹³ 2005	67M	C	WA	L D	SmCC+UCC	pT4	Lymph node	No	NU+PC+ E+Pt	6 months, alive with no recurrence
Onita ⁹ 2006	79F	J	H	L P	SmCC	pT3	No	No	NU	5 months, dead of cancer
Iizuka ⁹ 2006	69M	J	H	R M	SmCC+UCC	pT2	No	No	NU+EP+ Rad	3 years, dead of can- cer
Erick ¹² 2006	NA	A	NA	NA	SmCC	pT3	NA	NA	NU+ chemo	11 months, dead of cancer
Present case 2007	78M	J	H	R D	SmCC+UCC	pT3	Lymph node	malignant lymphoma	NU	3 months, alive with no recurrence

M: male; F: female; J: Japanese; K: Korean; C: Caucasian; A: American; H: hematuria; FP: flank pain; WA: wrongness of abdomen; L: left, R: right; P: proximal; D: distal; M: medium; SmCC: small cell carcinoma; UCC: urothelial cell carcinoma; SqCC: squamous cell carcinoma; AC: adenocarcinoma; CS: leiomyosarcoma; NU: nephroureterectomy; EP: etoposide+CDDP; TC: total cystectomy; CAP: cyclophosphamide+ADM+CDDP; PC: partial cystectomy; E: etoposide; Rad: radiation; MEC: MTX+epirubicin+CDDP; chemo: chemotherapy; Pt: platinum; NA: data not available

As of the time of writing, 3 months after surgery, the course of the patient has been uneventful. Closer follow-up is needed. Accumulation of such cases is expected to identify more effective therapies and techniques for earlier detection of ureteral small cell carcinoma.

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